THE DEVELOPMENT OF GENERAL METHODS FOR THE SYNTHESIS OF AZABICYCLO COMPOUNDS

BY

WILLIAM EDWARD GOODE

B.S., North Texas State College, 1946
M.S., North Texas State College, 1947

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
UNIVERSITY OF ILLINOIS, 1950

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Introduction

The reductive cyclization of nitro diesters over copper chromite catalyst at high temperatures and high hydrogen pressure has been employed by Leonard and coworkers[1] for the synthesis of certain 1-azabicyclo compounds. Since only γ-nitropimelic esters have been thus far readily obtainable, the method in general has been limited to the synthesis of pyrrolizidine (1-azabicyclo[3.3.0]octane) and substituted pyrrolizidines.

The greater flexibility allowed in the preparation of keto diesters prompted an investigation of the reductive cyclization of oximino diesters, with the oximino nitrogen as the incipient bridge-head of the final 1-azabicyclo compounds. This approach was expected to permit the convenient synthesis of bicyclic systems, not only of the pyrrolizidine type, but also of those containing other than five-membered rings.

An investigation of possible methods of preparation of two bicyclic amines containing a nitrogen atom at a position other than at the bridge-head was undertaken. These compounds, 9-azabicyclo[5.3.0]decane and 8-aza-9-phenylbicyclo-[5.3.0]decane, were of interest as possible precursors of aza-azulenes.

Discussion of Results

δ-Ketoazelaic acid has been prepared by the dialkylation of diethyl acetonedicarboxylate with ethyl β-iodopropionate, followed by hydrolysis and decarboxylation of the resulting tetracarboxylic ester.[2] γ-Ketopimelic acid,[3] 6-ketohendecanedioic acid,[4] and 7-ketotridecanedioic acid[4] have been synthesized in a similar manner, by alkylation of diethyl acetonedicarboxylate with ethyl bromoacetate, ethyl γ-iodobutyrate,

and ethyl δ-iodovalerate, respectively. These syntheses were repeated successfully, and the method was extended to include the preparation of 8-ketopentadecanedioic acid and 13-ketopentacosanedioic acid.

Several unsymmetrical keto diacids were prepared by the alkylation of diethyl acetonedicarboxylate with two different ω-halogen esters. It was found to be necessary to isolate the intermediate monoalkylation product before carrying out the reaction with the second ω-halogen ester.

Application of the reductive cyclization method to the oximino diesters derived from the keto diacids has lead to the formation, in good yield, of pyrrolizidine, quinolizidine, octahydropyrrocoline, 1-azabicyclo[5.3.0]decane, 1-azabicyclo-[5.4.0]hendecane, and 1-azabicyclo[5.5.0]dodecane. The excellent yields of the bicyclic amines containing seven-membered rings indicate that this method of synthesis is superior to those previously reported in the literature for these compounds.[5,6] The facile formation of compounds containing seven-membered rings prompted an investigation of the applicability of the reductive cyclization method to the synthesis of bicyclic systems containing even larger rings. However, attempts to prepare 1-azabicyclo[6.6.0]tetradecane, 1-azabicyclo[7.7.0]hexadecane, 1-azabicyclo[12.12.0]hexacosane by the reduction of the appropriate oximino diesters gave none of the desired bicyclic amines.

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VITA

The author was born in Denton, Texas, on July 20, 1923, and attended the public schools of that city. He was graduated from Denton Senior High School in June, 1940, and entered North Texas State College, Denton, Texas, in September of that year. His education was interrupted in 1942, when he became a member of the United States Army Air Force. Upon retirement to inactive duty in November, 1945, he returned to North Texas State College, and received the degree of Bachelor of Science in June, 1946, and the degree of Master of Science in June, 1947. He entered the Graduate College of the University of Illinois in September, 1947. He held teaching assistantships from September, 1947 to February, 1949, and the Eli Lilly Research Fellowship from September, 1949 to June, 1950.

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